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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/748,003	12/30/2003	Nejat K. Egilmez	40543.0001	6565

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EXAMINER	
FETTEROLF, BRANDON J	
ART UNIT	**PAPER NUMBER**
1642	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/24/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/748,003	EGILMEZ, NEJAT K.	
	Examiner	Art Unit	
	Brandon J. Fetterolf, PhD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *12-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/13/2006 has been entered.

Claims 1-26 are currently pending.

Claims 12-26 are withdrawn from consideration as being drawn to non-elected inventions.

Claims 1-11 are under consideration.

Response to Amendment

The Declaration under 37 CFR 1.132 filed by Richard Bankert on 11/13/2006 is insufficient to overcome the rejection of claims 1-11 under 35 U.S.C. 103(a) as being unpatentable over Mathiowitz et al. (US 2001/0043914, 2001) and Giardiello et al. (Gut, 1996; 38; 578-581) in view of Mathiowitz et al. (6,235,313, 2001) as set forth in the last Office action because: while the Dr. Bankert declaration sets forth that the combination of the two would not typically be considered as a therapeutic approach because it would be expected that the effects of the two would cancer out, the Examiner recognizes that each the two agents have been individually taught in the prior art to be effective at treating tumors, in particular gastrointestinal tumors.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mathiowitz et al. (US 2001/0043914, 2001, of record) and Giardiello et al. (Gut, 1996; 38; 578-581, of record) in view of Mathiowitz et al. (6,235,313, 2001, of record).

Mathowitz et al. ('914) teach a method of treating a tumor comprising administering to an individual a formulation comprising a polymeric microsphere containing IL-12, wherein the administration of the formulation is effective to treat said tumor (abstract). With regards to the polymeric microsphere, the '914 publication teaches that polymeric microsphere refers to polymeric particles including, but not limited to, polyanhydrides such as poly(lactide-co-glycolide), polycaprolactone, poly(fumaric-co-sebacic)acid and polyacrlylic acid (page 5, paragraph 0047 to 0049 and page 12, paragraph 0105). With regards to the tumor, Mathowitz et al. teach that the tumors include, but are not limited to, colon and rectum cancer, and esophageal cancer (page 4, paragraph 0043). With regards to the polymeric microsphere, Mathowitz et al teach that the polymeric microspheres can be prepared by a phase inversion nanoencapsulation method (page 6, paragraph 0057). In addition, the '914 publication teaches a method of inhibiting tumor growth comprising administering a microparticle preparation containing IL-12 during a chemotherapeutic procedure, such as agents which function to inhibit a cellular activity which the cancer cell is dependent upon for continued survival (page 16, 2nd column, claims 32 and 34 of the PGPub and page 8, paragraph 0075)further teaches that the concentration of the IL-12 microspheres may be at a dose of about 0.2-70 micrograms for an adult of 70Kg body weight or at a dose of 3.5-21 micrograms (page 11, paragraph 0092).

Giardiello et al. teach a method of inhibiting the growth of colorectal adenomas comprising the steps of orally administering sulindac to an individual with a gastrointestinal tumor in an amount effective to inhibit the growth of the tumor (Abstract). With regards to the effective amount, the reference teaches that 150 mg of sulindac was given per dose (Abstract, *Results*).

Neither Mathowitz et al. ('914) or Giardiello et al. teach the combination of IL-12 and sulindac for the treatment of gastrointestinal tumors. Moreover, Mathowitz et al. do not explicitly teach that the formulation comprising a polymeric microsphere containing IL-12 is administered orally or that the polymeric microspheres are prepared by hot melt method. Giardiello et al. does not explicitly teach that sulindac is encapsulated in a polymeric microsphere or any of the properties recited therein.

Mathowitz et al. ('313) teach bioadhesive microspheres for use in drug delivery systems, wherein the microspheres can be composed of bioerodible polymers such as polyanhydrides, poly[lactide-co-glycolide] and polyothoesters (column 7, lines 22-23). With regards to the microspheres, the patent teaches that the microspheres can be fabricated from different polymers using a variety of different methods including, but not limited to, hot melt microencapsulation (column 11, line 55 to column 12, line 55). Mathowitz et al. further disclose that the agents may be administered orally, wherein oral administration is advantageous with respect to both cost considerations as well as patient compliance and comfort (column 3, lines 50-57). Mathowitz et al. further teach that the bioadhesive molecules provide a drug delivery formulation that is useful for drug delivery via the mucosal membranes providing greater drug bioavailability (column 3, lines 50-60).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the polymeric microsphere containing IL-12 as taught by Mathowitz et al. ('914) and sulindac as taught by Giardiello et al. because each of the therapeutics had been individually taught in the prior art to be successful at treating gastrointestinal cancer. As such, the instant situation is amenable to the type of analysis set forth in In re Kerkhoven,205 USPQ 1069 (CCPA 1980) wherein the court held that it is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to for a third composition that is to be used for the very same purpose since the idea of combining them flows logically from their having been individually taught in the prior art. In addition, one would have been motivated to do so because Mathowitz et al. ('914) already teaches the combination of IL-12 with another agent which functions to inhibit a cellular activity which the cancer cell is dependent upon for continued survival. Thus, one of ordinary skill in the art would have reasonable expectation of success that by administering a composition comprising IL-12 and sulindac, one would achieve an effective treatment of gastrointestinal tumors. Secondly, the strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. In re Sernaker, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983).

Furthermore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to encapsulate the orally administered sulindac as taught by Giardiello et al. in a polymeric microsphere; and further, to administer the encapsulated IL-12 as taught by Mathowitz et al. ('914) and sulindac orally in view of Mathowitz et al. ('313) teachings that oral administration of polymeric microspheres provide greater drug bioavailability via the mucosal membranes and offers advantages over systemic injection with respect to cost considerations as well as patient compliance and comfort. One would have been motivated to do so because as taught by Mathowitz et al. ('313), oral administration of polymeric microspheres provide greater drug bioavailability via the mucosal membranes and offers advantages over systemic injection with respect to cost considerations as well as patient compliance and comfort. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by encapsulating sulindac in a polymeric microsphere and orally administering a combination of encapsulated sulindac and IL-12, one would achieve a method of providing a combination of encapsulated sulindac and IL-12 to a patient with greater bioavailability and patient compliance.

In response to this rejection, Applicants assert that neither of the cited references of Mathiowitz ('914) or Giardiello teach or even suggest the administration of the combination of IL-2 and sulindac and disagree with the Examiner that it would have been obvious for one skilled in the art to combine the two agents. In particular, Applicants point out that sulindac is an anti-inflammatory agent while IL-12 is a pro-inflammatory agent, and therefore, it would not occur to one skilled in the art to administer the two agents together because of their counter actions. In support of this contention, Applicants assert that the 1.132 Declaration by an expert in the field, Dr. Richard Bankert, makes clear that one skilled in the art would not consider such a therapeutic approach. Similarly, Applicants contend that one skilled would not consider combining the two agents for oral administration.

These arguments have been carefully considered, but are not found persuasive.

In response to Applicants assertion that the cited reference do not teach or suggest the administration of the combination of IL-12 and Sulindac; and further, oral administration of the two agents, the Examiner recognizes that it must be remembered that the references are relied upon in combination and are not meant to be considered separately as in a vacuum. It is the combination of all of the cited and relied upon references which made up the state of the art with regard to the

claimed invention. Applicant's claimed invention fails to patentably distinguish over the state of the art represented by the cited references taken in combination. In re Young, 403 F.2d 754, 159 USPQ 725 (CCPA 1968); In re Keller 642 F.2d 413,208 USPQ 871 (CCPA 1981). Furthermore, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference and it is not that the claimed invention must be expressly suggested in any one or all of the references; but rather the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). In the instant case, both IL-12 and sulindac have been individually taught in the prior art, e.g., Mathiowitz and Giardiello, to be effective at treating gastrointestinal tumors. Thus, it would have been *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to for a third composition that is to be used for the very same purpose since the idea of combining them flows logically from their having been individually taught in the prior art. Moreover, as taught by Mathowitz et al. ('313), oral administration of polymeric microspheres provide greater drug bioavailability via the mucosal membranes and offers advantages over systemic injection with respect to cost considerations as well as patient compliance and comfort. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by encapsulating sulindac in a polymeric microsphere and orally administering a combination of encapsulated sulindac and IL-12, one would achieve a method of providing a combination of encapsulated sulindac and IL-12 to a patient with greater bioavailability and patient compliance.

Therefore, NO claim is allowed.

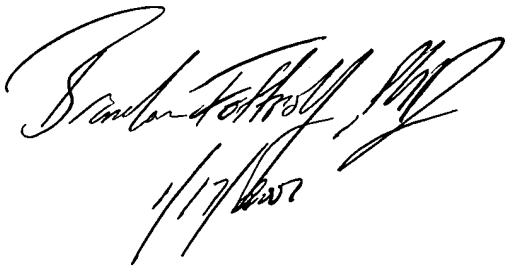
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Brandon J Fetterolf, PhD
Patent Examiner
Art Unit 1642

BF



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